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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,053	04/06/2000	James W. Williams	29666/35415	1413

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EXAMINER	
WANG, SHENGJUN	
ART UNIT	PAPER NUMBER
1617	17

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/529,053	Applicant(s) WILLIAMS ET AL.	
	Examiner Shengjun Wang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of applicants' declarations, amendments and remarks submitted June 30, 2003 is acknowledged.

Claim Rejections 35 U.S.C. 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 16, 17, 20, 21, 24, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870).

3. Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved. The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. See, particularly, column 3, lines 7-16.

1. Weithmann et al. does not teach expressly the amount effective to inhibit viral virion assembly. However, the optimization of a result effective parameter, e.g., effective amount for a therapeutical dosage of a known therapeutical agent, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. Further, treating a disease with an agent in a host would lead the agent contacting the pathogenic cell. A method known to be useful for treating viral infection would have been reasonably expected to be useful for prophylactic purpose. Further, known anti-viral agents would have been reasonably expected to be effective in

vitro against virus. Finally, since leflunomide is effective against virus through different mechanism, it would have been reasonably expected to effective against those virus with resistance to antiviral agent that inhibit viral DNA replication. As to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Flamand et al.

Claim 19 is obvious for reasons discussed above and in further view of Flamand et al. Weithmann et al. do not teach expressly the method for treating herpes.

4. However, Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. See, particularly, the abstract.

5. Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Weithmann for treating herpes infections.

6. A person of ordinary skill in the art would have been motivated to employ the method of Weithmann for treating herpes infections, because herpes infection is known to be involved interleukin 1 beta.

7. Claims 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

8. Claims 22 and 23 are obvious over Weithmann et al. as discussed above, and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

Weithmann et al. do not teach expressly the employment of addition antiviral agent in the method.

9. However, Hammer teaches that several pyrimidin compounds are known antiviral agents. See, particularly, page s3.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as those known pyrimidin compounds Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Claims 16-20, 21, 24, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095) in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722).

10. Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, the compounds have similar biological activity of leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. The expressly taught compounds includes those meet the leflunomide products (page 18-19 in the

specification). Homologue of leflunomide (e.g., 5-methyl-isoxazole-4-carboxylic acid 2,2,2,trifloroethylamide) have been expressly disclosed (page 10, line 35). These compounds are known to be useful for treating or preventing viral infection such as hepatitis and cytomegalovirus infection, particularly, HCMV. See, page 4, lines 23-32.

11. Coghlan et al. does not teach expressly the employment leflunomide or its metabolite, or the particular amount herein for treating viral infections.

12. However, McChesney et al. teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. See, particularly, the abstract at page 1717, and the materials and method at page 1717-1718.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV.

2. A person of ordinary skill in the art would have been motivated to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV because these compounds are known to be useful for treating or preventing viral infection, and both leflunomide and A771726 are known to be similarly useful as the other compounds. Further the reference teaches certain compounds that are structural homologs of the instantly claimed leflunomide, i.e., they differ only by a CH_2 group. The instant compounds are structural homologs of the reference compounds when they differ only by a CH_2 group. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compound because such structurally homologous compounds are

expected to possess similar properties. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. In re Hass, 60 USPQ 544 (CCPA 1944); In re Henze, 85 USPQ 261 (CCPA 1950). Finally, since leflunomide is effective against virus through different mechanism, it would have been reasonably expected to effective against those virus with resistance to antiviral agent that inhibit viral DNA replication. As to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095) in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722), and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

Coghlan et al. (WO 94/24095), and McChesney et al. do not teach expressly the employment of addition antiviral agent in the method.

13. However, Hammer teaches that several pyrimidin compounds are known antiviral agents. See, particularly, page s3.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as those known pyrimidin compounds Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral

agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Response to the Arguments

Applicants' amendments remarks and declaration submitted June 26, 2003 have been fully considered, but are not persuasive for reasons discussed below.

14. The declaration under 37 CFR 1.132 filed June 26, 2003 is insufficient to overcome the rejection of claims 16, 17, 19-25 based upon Weithmann et al. as set forth in the last Office action because: applicants' attack of Weithmann reference is not probative. Particularly, Weithmann specifically claimed method of treating HIV infection hepatitis with one of leflunomide products. Further, Since every patent is presumed valid (35 U.S.C. 282), and since that presumption includes the presumption of operability (Metropolitan Eng. Co. v. Coe, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935), examiners should not express any opinion on the operability of a patent. Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). (See, also, MPEP 716.07).

15. The declaration by Edward s. Mocarski under 37 CFR 1.132 filed June 26, 2003 is insufficient to overcome the rejection of claims 16-25 based upon Coghlan et al. in view of McChesney et al. as set forth in the last Office action because: The rejections are based on the cited references as whole, not solely based on McChesney. The examiner agrees that McChesney

does not teach or suggest conclusively that leflunomide is antiviral active. However, in view the totality of cited references, the claims are obvious as discussed above.

16. Applicants' arguments that Weithmann reference is not enabled for treating viral infection is not persuasive for reasons set forth above.

3. Applicants allege that Coghlan, or McChesney does not teach the isoxazole compounds structurally related to leflunomide products inhibit viral replication, and therefore, the claimed invention is not obvious over Coghlan, and McChesney. These arguments are not persuasive. The examiner agrees that Coghlan, or McChesney does not teach the isoxazole compounds structurally related to leflunomide products inhibit viral replication. However, the claimed method which read on treating patient infected with HIV, hepatitis, or herpes is obvious over Coghlan, or McChesney. As stated above, to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct. The instant claims are directed to effecting a biochemical pathway with an old and well known compounds. The argument that such claims are not directed to the old and well known ultimate utility (antiviral) for the compounds, e.g., leflunomide, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered functionary property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." Additionally, where the patent Office has reason to believe that a functionally limitation asserted to be critical for establishing novelty in the claimed subject matter may, in

fact, be an inherent characteristic of the prior art, it possesses the authority to requires the applicant to prove that the subject matter shown to be in the prior art does not posses the characteristic relied on. In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

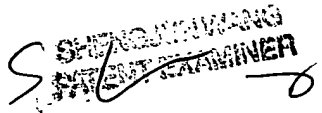
4. Applicant alleges that no data in the literature or in practically that correlate immunosuppressive effect to useful anti-viral activity. The allegation is not probative in overcome the rejections over Coghlan, and McChesney. Particularly, Coghlan teaches novel compounds having immunomodulatory activity (see the field of invention, page 1). And the compounds are known to be useful for treating patients with viral infections. The compounds may, or may not have direct antiviral activity, but they are known to useful for treating patients with viral infection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang, Ph.D. whose telephone number is (703) 308-4554. The examiner can normally be reached on Monday-Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Patent Examiner



Shengjun Wang

September 19, 2003